

The reaction of aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione under solvent-free grinding conditions

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The reaction of aromatic aldehyde **1** and 5,5-dimethyl-1,3-cyclohexanedione **2** under solvent-free and solid state conditions has been catalyzed by $\text{KF}/\text{Al}_2\text{O}_3$ or silica sulfate and yields two products: 2,2'-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one) **3** and 1, 8-dioxooctahydroxanthene **4** and their derivatives. In addition, 2-amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran **5** is also obtained in this condition. This method provides several advantages such as good yield (61-93%), simple work-up procedure and is environment friendly.

Keywords: aromatic aldehydes, 5,5-dimethyl-1,3-cyclohexanedione, 2,2'-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one), 1, 8-dioxooctahydroxanthene

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Solid reaction without using harmful organic solvents is of great current interest especially in relation to environmental concerns today. So, the grinding method has increasingly been used in organic synthesis in recent years. Compared to traditional methods, many organic reactions occur more efficiently in the solid state than in solution and in some cases even more selectively¹. A large number of organic reactions can be carried out in high yield under mild conditions and simply by this method such as oxidation², reduction³, rearrangement⁴, coupling reactions⁵, aldol condensations⁶ and the Michael reaction⁷.

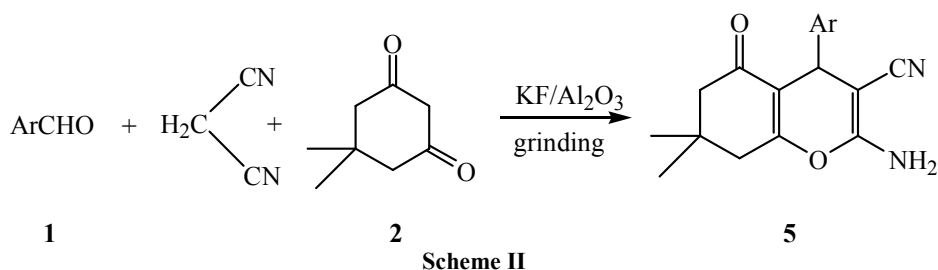
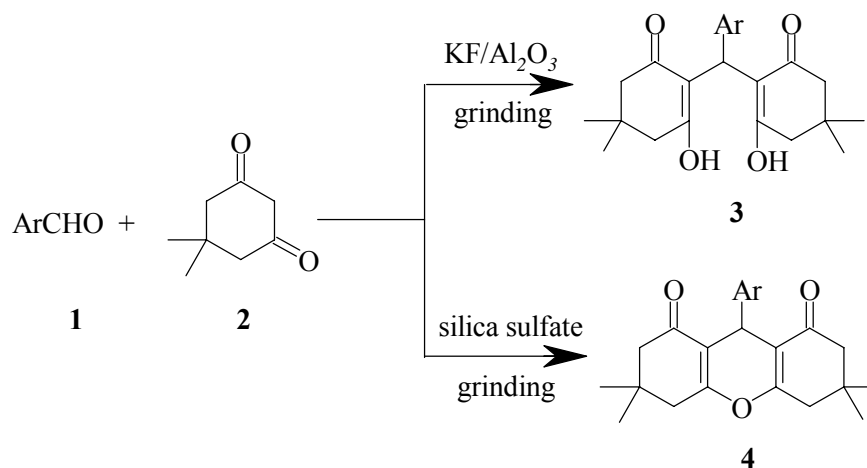
As a methylene active compound, 5,5-dimethyl-1,3-cyclohexanedione has been used in many organic reactions⁸. It has been reported that the reaction of aromatic aldehyde and 5,5-dimethyl-1,3-cyclohexanedione can yield 2,2'-arylmethylene bis (3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) and 1,8-dioxooctahydroxanthene and their derivatives by many methods. However, the use of $\text{KF}/\text{Al}_2\text{O}_3$ or silica sulfate as the catalyst in the solid state for the synthesis of 2,2'-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) **3** and 1,8-dioxooctahydroxanthene **4** and their derivatives has not been reported. In this manuscript, we report herein, a general and highly efficient route for the synthesis of these two products and their derivatives using an

inexpensive and commercially available $\text{KF}/\text{Al}_2\text{O}_3$ and silica sulfate as catalyst. This is an efficient synthesis in solid state, not only preserves the simplicity but also consistently gives the corresponding products, 2,2'-arylmethylenebis (3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one) **3** and 1,8-dioxooctahydroxanthene **4** in good yields (**Scheme I**).

As shown in **Scheme I**, the different products were obtained using different catalysts in this reaction. In a typical general experimental procedure, aromatic aldehyde **1** and 5,5-dimethyl-1,3-cyclohexanedione **2** were grinded in the presence of a catalytic amount of $\text{KF}/\text{Al}_2\text{O}_3$ or silica sulfate, the corresponding products **3** and **4** were obtained in good to excellent yields.

At the same time, we also found that if we changed a molecule 5,5-dimethyl-1,3-cyclohexanedione **2** to malononitrile, the reaction also could be catalyzed by $\text{KF}/\text{Al}_2\text{O}_3$ in the same conditions and obtained 2-amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyrans **5** (**Scheme II**).

To study the generality of the process, several examples illustrating this method for the synthesis of **3**, **4** and **5** were studied. The results are summarized in **Table I**. The effect of electron and the nature of substituents on the aromatic ring did not show strongly obvious effects in terms of yields under these reaction conditions. The reaction proceeded smoothly under this condition to give the corresponding

**Table I** — The results of the solid condensation

S.No	Ar	Product	Yield ^a (%)	m.p./ °C	
				Found	Reported ⁸
a	C ₆ H ₅	3a	86	192-94	194-95
		4a	91	200-01	202-04
		5a	85	227-28	229-31
b	4-ClC ₆ H ₄	3b	94	145-47	
		4b	92	229-31	228-30
		5b	89	207-09	208-10
c	3-ClC ₆ H ₄	3c	92	188-90	
		4c	88	185-87	183-84
		5c	86	222-25	224-25
d	2-ClC ₆ H ₄	3d	93	202-04	205
		4d	82	232-35	228-30
		5d	79	213-15	217-18
e	2,4-Cl ₂ C ₆ H ₃	3e	89	203-05	
		4e	77	249-51	253-54
f	4-O ₂ NC ₆ H ₄	3f	91	195-96	188-90
		4f	76	223-25	226-28
		5f	83	175-77	177-78
g	3-O ₂ NC ₆ H ₄	3g	91	201-03	197-98
		4g	94	171-73	168-70
		5g	87	213-14	208-11
h	4-CH ₃ C ₆ H ₄	3h	89	141-43	
		4h	79	219-20	217-18
		5h	82	213-15	208-10

— Contd

Table I — The results of the solid condensation — *Contd*

S.No	Ar	Product	Yield ^a (%)	m.p./ °C	
				Found	Reported ⁸
i	4-CH ₃ OC ₆ H ₄	3i	90	146-48	142-43
		4i	88	240-41	242-44
		5i	95	195-97	199-01
j	4-HOC ₆ H ₄	3j	90	201-03	188-90
		4j	76	244-45	246-48
		5j	84	211-12	214-15
k	3,4-(OCH ₂ O)C ₆ H ₃	3k	92	187-89	175.5-77
		4k	84	219-20	224-26
		5k	90	209-12	211-13
l	4-HO-3-CH ₃ OC ₆ H ₃	3l	89	193-95	195.5-96.5
		4l	64	224-25	226-28
		5l	61	239	237-39

^a Isolate yield.

products in good yields. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups or electron-donating groups were employed and reacted well to give the corresponding **3**, **4** and **5** in good to excellent yields.

Taking the reaction of **b** and **i** as the example, we investigated the effect of the catalysts on these reactions. It was found that they played a crucial role in the success of the reactions in terms of the rate and the yields. The results are summarized in **Table II**.

From **Table II**, we can see that the effect of the amount of the catalyst on these reactions is important. In the absence of the catalyst, the reaction (**1+2**→**4**) could not be carried out. The else two reactions gave very poor yield (<65%). By changing the amount of the catalyst, higher yields were obtained. As shown in **Table II**, we can choose the best quantitative catalyst for these reactions.

The catalyst KF/Al₂O₃ or silica sulfate can be reused after simple heating at 120 °C for 4hr. We have successfully used the recycled KF/Al₂O₃ to catalyze the synthesis of **5i**, the yield of which is excellent.

All of the compounds prepared were characterized by ¹H NMR and IR analyses.

In summary, a procedure for the preparation of 2,2'-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one), 1,8-dioxooctahydroxanthene, 2-amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran and their derivatives have been developed. It is noteworthy that the experimental procedure is very simple, and strict anhydrous conditions are not required. In addition, high temperature is not needed. This report has proposed

Table II — The effect of the catalysts on the reactions

Product	Yield (%) ^a	Yield (%) ^b	Yield (%) ^c	Yield (%) ^d	Yield (%) ^e
3b	64	78	94	89	85
4b	0	79	88	92	91
5b	59	81	89	82	79
3i	62	69	90	81	77
4i	0	79	81	88	82
5i	60	73	95	89	82

^ano catalyst; ^bthe quantity of the aldehyde: catalyst is 1mmole: 25 mg. ^cthe quantity of the aldehyde: catalyst is 1mmole: 50 mg. ^dthe quantity of the aldehyde: catalyst is 1mmole: 75 mg. ^ethe quantity of the aldehyde: catalyst is 1mmole: 100 mg.

and demonstrated a new useful and attractive process for the synthesis of these compounds.

Experimental Section

General. Liquid aldehydes were distilled before use. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ¹H NMR spectra were measured on a Bruker AVANCE 400 (400 MHz) spectrometer using TMS as internal reference and CDCl₃ as solvent. Melting points are uncorrected.

Preparation and activation of KF/Al₂O₃. The catalyst, KF/Al₂O₃ was prepared by dissolving 20g KF in 80 mL water and 30 g basic Al₂O₃. The mixture was stirred at 65~75 °C for 1hr and the water was removed under reduced pressure. The resulting free flowing powder was dried at 120 °C for 4hr. The content of KF is about 30%.

Preparation of silica sulfate⁹. A 500 mL suction flask was used. It was equipped with a constant pressure dropping funnel containing of chlorosulfonic acid (58.3g, 0.5 mole) and gas inlet tube for conducting of HCl gas over an absorbing solution i.e., water. It was charged silica gel (100 g) and CH₂Cl₂ (50 mL). Chlorosulfonic acid was added dropwise over a period of 30 min under stirring at room temperature. HCl gas was evolved from reaction vessel immediately. After the addition was complete, the mixture was shaken for 60 min and the solvents, CH₂Cl₂ and HCl were evaporated under reduced pressure. A white solid (silica sulfate, 120.0 g, ~100%) was obtained, and finally stored in a desiccator until use.

General procedure for the preparation of 3 and 4. Aromatic aldehyde (2 mmoles), 5,5-dimethyl-1,3-cyclohexanedione (4 mmoles) and KF/Al₂O₃ (100 mg) or silica sulfate (150 mg) were added to a mortar. The mixture was ground by mortar and pestle at room temperature for 20~40 min, and was kept at room temperature for a period (14-20 hr). The completion of the reaction was monitored with TLC. The product was extracted with dichloromethane and filtered; the solvent was evaporated under reduced pressure. The products **3** and **4** obtained was recrystallised from 95% EtOH.

General procedure for the preparation of 5. Aromatic aldehyde (2 mmoles), 5,5-dimethyl-1,3-cyclohexanedione (2 mmoles), malononitrile (2 mmoles) and KF/Al₂O₃ (100 mg) were added to a mortar. The mixture was ground by mortar and pestle at room temperature for 40 min, and kept at room temperature for a period (14-20 hr). The completion of the reaction was monitored with TLC. The product was extracted with dichloromethane and filtered; the solvent was evaporated under reduced pressure. The product **5** obtained was recrystallised from 95% EtOH. Data of some compounds are shown below:

3b: IR (KBr): 3420, 3050, 2946, 2868, 2599, 1588, 1458, 1400, 1368, 1298, 1236, 1133, 1055, 974, 870, 789 cm⁻¹; ¹H NMR: δ 1.11 (s, 6H, 2 × CH₃), 1.22 (s, 6H, 2 × CH₃), 2.31-2.54 (m, 8H, 4 × CH₂), 5.47 (s, 1H, CH), 6.97-7.29 (m, 4H, Ar-H), 11.58 (br, s, 1H, OH), 11.93 (br, s, 1H, OH); Anal. Calcd for C₂₃H₂₇ClO₄: C, 68.56; H, 6.25. Found: C, 68.78; H, 6.09 %.

3c: IR (KBr): 3423, 3048, 2950, 2871, 2622, 1587, 1470, 1423, 1377, 1299, 1246 1151, 1066, 974, 890, 870, 789 cm⁻¹; ¹H NMR: δ 1.11 (s, 6H, 2 × CH₃), 1.23 (s, 6H, 2 × CH₃), 2.33-2.53 (m, 8H, 4 × CH₂), 5.53 (s,

1H, CH), 7.02-7.31 (m, 4H, Ar-H), 11.59 (br, s, 1H, OH), 11.89 (br, s, 1H, OH); Anal. Calcd for C₂₃H₂₇ClO₄: C, 68.56; H, 6.25. Found: C, 68.78; H, 6.12 %

3e: IR (KBr): 3423, 3060, 2955, 2865, 2630, 1601, 1468, 1417, 1379, 1313, 1250, 1152, 1140, 975, 889, 871, 795 cm⁻¹; ¹H NMR: δ 1.11 (s, 6H, 2 × CH₃), 1.23 (s, 6H, 2 × CH₃), 2.30-2.52 (m, 8H, 4 × CH₂), 5.53 (s, 1H, CH), 7.02-7.23 (m, 3H, Ar-H), 11.57 (br, s, 1H, OH), 11.93 (br, s, 1H, OH); Anal. Calcd for C₂₃H₂₆Cl₂O₄: C, 63.16; H, 5.99. Found: C, 63.01; H, 5.86 %.

3h: IR (KBr): 3424, 3059, 2960, 2870, 2628, 1615, 1471, 1419, 1380, 1259, 1166, 1144, 1001, 890, 840, 790, 750, 718 cm⁻¹; ¹H NMR: δ 1.12 (s, 6H, 2 × CH₃), 1.24 (s, 6H, 2 × CH₃), 2.31-2.51 (m, 8H, 4 × CH₂), 5.47 (s, 1H, CH), 2.78 (s, 3H, CH₃Ar), 6.92-7.21 (m, 3H, ArH), 11.57 (br, s, 1H, OH), 11.91 (br, s, 1H, OH); Anal. Calcd for C₂₄H₃₀O₄: C, 73.36; H, 7.91. Found: C, 73.58; H, 7.68 %.

4a: IR (KBr): 3030, 2980, 1685, 1670, 1470, 1360, 1200, 1170, 1140, 1005, 740, 700 cm⁻¹; ¹H NMR: δ 0.98 (s, 6H, 2 × CH₃), 1.13 (s, 6H, 2 × CH₃), 2.21 (dd, 4H, *J* = 1.6, *J* = 2.4, 2 × CH₂, H-4, 5), 2.43 (s, 4H, 2 × CH₂, H-2, 7), 4.68 (s, 1H, H-9), 7.21 (m, 5H, Ar-H). Anal. Calcd for C₂₃H₂₆O₃: C, 78.83; H, 7.47. Found: C, 78.91; H, 7.44 %.

4b: IR (KBr): 3028, 2980, 1680, 1660, 1620, 1490, 1480, 1360, 1200, 1170, 1140, 1090, 1010, 1000, 850, 840 cm⁻¹; ¹H NMR: δ 0.98 (s, 6H, 2 × CH₃), 1.11 (s, 6H, 2 × CH₃), 2.23 (dd, 4H, *J* = 1.6, *J* = 3.0, 2 × CH₂, H-4, 5), 2.51 (s, 4H, 2 × CH₂, H-2, 7), 4.65 (s, 1H, H-9), 7.28-7.44 (m, 4H, ArH). Anal. Calcd for C₂₃H₂₅ClO₃: C, 71.77; H, 6.54. Found: C, 71.85; H, 6.43 %.

4c: IR (KBr): 3030, 2980, 1685, 1660, 1620, 1490, 1475, 1365, 1200, 1170, 1135, 1095, 1000, 850, 840 cm⁻¹; ¹H NMR: δ 1.00 (s, 6H, 2 × CH₃), 1.13 (s, 6H, 2 × CH₃), 2.31 (dd, 4H, *J* = 1.6, *J* = 3.2, 2 × CH₂, H-4, 5), 2.47 (s, 4H, 4 × CH₂, H-2, 7), 4.78 (s, 1H, H-9), 7.13-7.25 (m, 4H, ArH). Anal. Calcd for C₂₃H₂₅ClO₃: C, 71.77; H, 6.54. Found: C, 71.89; H, 6.45 %.

4d: IR (KBr): 3030, 2980, 1680, 1665, 1620, 1495, 1470, 1360, 1200, 1170, 1140, 1100, 1000, 850, 840 cm⁻¹; ¹H NMR: δ 0.98 (s, 6H, 2 × CH₃), 1.10 (s, 6H, 2 × CH₃), 2.08 (dd, 4H, *J* = 1.6, *J* = 3.0, 2 × CH₂, H-4, 5), 2.50 (s, 4H, 2 × CH₂, H-2, 7), 4.63 (s, 1H, H-9), 7.26-7.35 (m, 4H, ArH). Anal. Calcd for C₂₃H₂₅ClO₃: C, 71.77; H, 6.54. Found: C, 71.85; H, 6.39 %.

4e: IR (KBr): 3035, 2980, 1685, 1660, 1633, 1490, 1480, 1410, 1360, 1210, 1195, 1155, 1100, 1000, 850, 770 cm^{-1} ; ^1H NMR: δ 1.01 (s, 6H, $2 \times \text{CH}_3$), 1.13 (s, 6H, $2 \times \text{CH}_3$), 2.25 (dd, 4H, $J = 1.6$, $J = 3.4$, $2 \times \text{CH}_2$, H-4, 5), 2.49 (s, 4H, $2 \times \text{CH}_2$, H-2, 7), 4.98 (s, 1H, H-9), 7.20 (s, 1H, ArH), 7.38 (d, 2H, $J = 8.4$, ArH). Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{Cl}_2\text{O}_3$: C, 65.87; H, 5.73. Found: C, 65.99; H, 5.62 %.

4h: IR (KBr): 3030, 2980, 1665, 1650, 1623, 1530, 1360, 1340, 1200, 1070, 1042, 1005, 875, 833 cm^{-1} ; ^1H NMR: δ_{H} 1.00 (s, 6H, $2 \times \text{CH}_3$), 1.14 (s, 6H, $2 \times \text{CH}_3$), 2.18 (dd, 4H, $J = 1.6$, $J = 3.0$, $2 \times \text{CH}_2$, H-4, 5), 2.44 (s, 4H, $2 \times \text{CH}_2$, H-2, 7), 4.48 (s, 1H, H-9), 7.52-7.64 (m, 2H, ArH), 8.08-8.16 (m, 2H, ArH). Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_5$: C, 69.85; H, 6.37; N, 3.54. Found: C, 69.92; H, 6.45; N, 3.43 %.

4i: IR (KBr): 3025, 2980, 1685, 1660, 1620, 1513, 1450, 1375, 1360, 1260, 1235, 1170, 1142, 1032, 1003, 840 cm^{-1} ; ^1H NMR: δ 1.01 (s, 6H, $2 \times \text{CH}_3$), 1.13 (s, 6H, $2 \times \text{CH}_3$), 2.22 (dd, 4H, $J = 1.6$, $J = 2.4$, $2 \times \text{CH}_2$, H-4, 5), 2.49 (s, 4H, $2 \times \text{CH}_2$, H-2, 7), 3.75 (s, 3H, CH_3O), 4.73 (s, 1H, H-9), 6.66-7.26 (m, 4H, ArH). Anal. Calcd for $\text{C}_{24}\text{H}_{28}\text{O}_4$: C, 75.76; H, 7.41. Found: C, 75.83; H, 7.35 %.

5a: IR (KBr): 3390, 3290, 2935, 2200, 1685, 1600 cm^{-1} ; ^1H NMR: δ 0.98(3H, s, CH_3), 1.05(3H, s, CH_3), 2.15(1H, d, $J = 16.0\text{Hz}$, 8-H) 2.24(1H, d, $J = 16.0\text{Hz}$, 8-H), 2.45-2.55(2H, m, 6-H), 4.32(1H, s, 4-H), 6.08(2H, s, NH_2), 7.15-7.30 (5H, m, ArH); Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 72.99; H, 6.33; N, 9.33 %.

5b: IR (KBr): 3410, 3310, 3005, 2200, 1695, 1605 cm^{-1} ; ^1H NMR: δ 0.95(3H, s, CH_3), 1.04(3H, s, CH_3), 2.10(1H, d, $J = 16.0\text{Hz}$, 8-H) 2.25(1H, d, $J = 16.0\text{Hz}$, 8-H), 2.47-2.55(2H, m, 6-H), 4.20(1H, s, 4-H), 7.08(2H, s, NH_2), 7.17(2H, d, $J = 8.0\text{Hz}$, ArH) 7.35(2H, d, $J = 8.0\text{Hz}$, ArH); Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2$: C 65.75, H 5.21, N 8.52, Found C, 65.41, H, 5.21; Found: C, 65.41; H, 4.99; N, 8.12 %.

5i: IR (KBr): 3377, 3186, 2964, 2198, 1681, 1655, 1596 cm^{-1} ; ^1H NMR: δ 0.95(3H, s, CH_3), 1.03(3H, s, CH_3), 2.09(1H, d, $J = 16.0\text{Hz}$, 8-H), 2.24(1H, d, $J = 16.0\text{Hz}$, 8-H), 2.46-2.56(2H, m, 6-H), 3.71(3H, s, OCH_3), 4.17(1H, s, 4-H), 6.84(2H, d, $J = 8.0\text{Hz}$, ArH), 6.95(2H, s, NH_2), 7.05(2H, d, $J = 8.0\text{Hz}$, ArH); Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$: C 70.35; H 6.21, N 8.64. Found C, 70.01; H, 5.88, N, 8.30%.

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